Making the business case for continuous manufacturing in the pharmaceutical industry

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Abstract
On-going new technology development in continuous manufacturing (CM) has enabled the potential for significant step changes within the pharmaceutical sector i.e. shifting from ‘batch’ to ‘continuous’ processing. However, current adoption rates of CM remain at 5%. This research explores the supply network challenges and business case for CM.

Keywords: supply network, continuous manufacturing, pharmaceuticals

Introduction
Healthcare is an industry sector where remote diagnostics, ageing populations and new approaches to patient care will result in very different network configurations featuring increasingly distributed information flows and innovative revenue models. The Pharmaceutical sector in the UK is a significant industry in terms of employment (78,000 jobs) and turnover (£31bn in 2011) with impressive export growth (plus 31%, 2008-2011). Many UK based-firms have leading international positions and the sector is one of the Governments’ declared national priorities. A measure of the High-Value-Manufacturing character of the sector is the gross value added (GVA)/Employee which was £210/k per employee in 2011 (ONS data from 2012). Despite these strengths, the UK Pharma manufacturing sector has seen many site closures since the 1990s, with new manufacturing investments increasingly made offshore and a consequent loss in UK manufacturing jobs. This has been accompanied by the rapid growth in outsourced contract manufacturing, as production becomes an increasingly commoditized activity. The lack of investment and innovation in new production and supply chain models is somewhat surprising considering the commercial and technological imperatives that need to address potential market failures and the need for more flexible assets and integrated supply chains. Future supply models need to embrace emerging technologies where advances in stratified and personal medicines, for example, require a more diverse set of products, with lower volumes that serve smaller patient populations.

On-going new technology development in the area of ‘Continuous Manufacturing’ (CM) has enabled potential for significant step changes within the Pharmaceutical sector e.g.
shifting from traditional ‘batch’ to ‘continuous’ processing has implications for (a) product variety, consistency and functionality (b) energy and resource efficiency (c) inventory and customization options and (d) overall industry structure. While other industries, such as oil, gas, petrochemicals, polymers, and food currently operate in CM mode; extensive use of CM is still relatively new to the pharmaceutical industry where the current adoption rate of continuous processing is approximately 5%. Despite the fact that 50% of reactions could benefit from a continuous process based on e.g. micro-reactor technology, the industry still dominated by batch processes and it is estimated that rejected batches, rework and investigations can equate to as much as 25% of pharmaceutical company revenues. The focus of this paper is to explore supply network challenges to, and opportunities for, the adoption of CM – in order to inform and build the business case for further adoption.

Potential Market Failures and Commercial Opportunities

The current supply base is recognized as being inflexible and has been built to serve the large volume blockbuster model of the past. However, only recently, it has become clear that this model is obsolete. As a result there are potential market failures ahead in terms of:

• Current inflexible manufacturing capacity: no longer fit for purpose in supporting new products and treatments which require multiple supply solutions, that can sustain a broad range of product volumes and patient populations
• The emergence of new technologies and therapies are changing the manufacturing and supply chain landscape which require alternative production processing and business models (e.g. more continuous processes, novel enzymes, post-dosed actives, diagnostics), involving smaller production plants with more distributed local-to-market manufacturing options
• Distressed national health budgets and increasingly stretching patient health targets require more affordable treatments, that can no longer carry the costs of excessive inventory and batch processing quality failures that are estimated to cost the global industry £20bn/y.
• Drug and treatment complexity that require products that better facilitate patient compliance for improved patient outcomes. This situation can present an opportunity for those SCs that can re-invent themselves for this new context.

CM is a prime example where alternative processing in API and Formulation could generate multiple benefits e.g.

• Plant footprint reduction by 70%;
• CapEx reduction by 25%;
• Operating cost reduction by 30%;
• Yield improvement by 10%;
• More consistent quality; more controllable, repeatable processes.
• In combination these improvements could generate CO2 savings of 50% or more to improve industrial sustainability.

In addition, within the pack and distribute downstream SC, the design of more integrated and efficient SCs and patient friendly pack/APP solutions may reduce inventory and waste. In distribution there are opportunities to collaborate in developing multiple distribution models for the alternative product SCs that will emerge. This may involve new consolidation points,
so called ‘last mile’ rapid delivery systems, more effective cold-chain distribution models, and more reliable information chains to ensure right-first-time delivery. Adaptive SCs will be required that respond to more genuine demand signals rather than the current inventory heavy, long term forecast based models. Designing new and effective routes to emerging markets incorporating new technologies and new geographies – will require logistics analysis, design and delivery capabilities from sectors where replenishment models are both secure but more responsive to demand changes. In addition it is envisaged that there will be significant spillover effects to related process industries and service supply models where the adoption of new technologies will require alternative supply chain models. Specific commercial benefits have been estimated as follows;

- Cost reductions of 10% in drug development where costs are estimated at £0.6bn/drug
- Reduction in inventory from current levels – c. 200 days within primes – and >70 wks E2E; a 10% reduction would support savings in excess of £1bn in the UK (one off) or circa. £100m/y in reduced working capital
- Manufacturing quality performance levels, that are typically 3σ are well below the 6σ levels one might expect for similar processes; efficiency savings would be significant (estimated saving potential of £300m/y)
- Patient compliance, where data suggests this is far from optimal and improvement in treatment adherence can generate substantial benefits to patient outcomes and reduce waste

Research context

From a broader research context, many industries have witnessed the progressive ‘disaggregation’ of their value networks driven by specialization and the geographic dispersion of key activities (globalization). Although previous research has provided rich narratives on these changes to industry structure they do not provide direction on how to configure global value networks ‘end-to-end’. Different patterns of specialization and internationalization are expected to emerge, as firms seek to develop competitive positions across the value network, while seeking to integrate external capabilities and capture the benefits of location. In many sectors, the disruptive impacts of new technologies or novel business models have resulted in radically reconfigured value networks. Future markets will therefore require multiple SC models that can embrace emerging therapies – for example regenerative medicines that will require SCs that are yet to be invented.

Methodology and case example

A number of cases exploring intervention examples using this approach to develop new or radically different product-process reconfiguration models that can support major breakthroughs in total value network performance were examined. These included exploring continuous-processing and crystallization in previously batch-process-oriented Pharma, implications of additive manufacturing in component manufacture that replaces traditional subtractive processes, and post-dosing product finishing models that enable more near-market supply. Although none of these models examined have reached industrial viability, as each requires significant technology breakthroughs in formulation, production processing and/or delivery models, redesign alternatives and options were considered that might be suitably informed by a broader value network analysis and systems optimisation agenda. These conceptual network redesign studies emphasized different product, process and business
models that enable new or previously elusive markets to be served economically. In building the business case, the first stage involves exploration of current state process models with stage 2 aims to map/generate future process and network design options and scenarios involving (I this case) continuous candidate products. A 5-step process is proposed in order to build a business case for CM candidate products and is summarised in figure 1:

<table>
<thead>
<tr>
<th>Step</th>
<th>Candidate enquiry</th>
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<tbody>
<tr>
<td><strong>Step A</strong> Pre-screening</td>
<td>Basic data on candidate (e.g. Therapy Area, Patient Population, Treatment profile(s) Cost, Volumes) Rapid opportunity/barrier analysis - operational &amp; societal data Rapid volume/variety analysis Unmet needs (e.g. business context) Process chemistry (e.g. process pre-disposed to CM?)</td>
</tr>
<tr>
<td><strong>Step B</strong> Current State Process Model</td>
<td>SN configuration tools applied in specific context Plot the curves (by sub-system) - current state Workshop: Populate Opportunity Grid (i.e. potential benefits and outcomes matrix)</td>
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<tr>
<td><strong>Step C</strong> Future State Mapping</td>
<td>Clinical Trials Primary/Secondary Pack/Distribute E2E Workshop: Alternative process and network design options</td>
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<tr>
<td><strong>Step D</strong> Sub-system integration, business context weighting and technology feasibility</td>
<td>Analytical Framework (sub-systems) Output (i.e. Deltas) Business Context/Viability Technology Readiness</td>
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<td><strong>Step E</strong> Cross-case data analysis; emerging patterns etc.</td>
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**Figure 1.** 5-step process is proposed building a business case for CM candidate products

**Step A:** Pre-screening step where rapid assessment of proposed candidates is undertaken e.g. basic data on each potential candidate (see table 1) is gathered in terms of i) process chemistry and technical feasibility (is the current synthetic route pre-disposed to CM? What alternative synthetic routes could be?), ii) operational and societal data in order to perform rapid opportunity/barrier analysis, examine “affordability”, business context (what are the unmet needs and continuous cost advantages?) and supply network implications e.g.

- **Therapy Area/disease area** (e.g. Diabetes, Malaria)
- **Patient Population** (e.g. Global & Target)
- **Treatment Profile** (e.g. Dosage, Frequency, Duration)
- **Volumes** (current and future predictions)
- **Basic financials** (averages) - Price, Cost, Revenues, Margin etc.
- **SKU mix** (e.g. strengths, pack sizes)
- **Inventory** (e.g. total forward days cover)
- **CapEx** (e.g. investment for future requirement (batch) e.g. new capacity w/current paradigm)
- **Quality/Waste** (e.g. yield; kg waste per kg output)
Exploratory cases suggest that barriers may be real or perceived, and arise from combinations of socio-political, technical and regulatory factors. Hence, this step helps identify the barriers to adopting potential alternative product-process technologies and business models that might be used to serve existing markets more effectively or deliver unmet end-user needs. Unmet end-user needs, on the other hand, are either driven by new capabilities that create new markets or known market or segments that have been previously considered uneconomical to serve. Personalized medicines or niche product markets were examples where advances in diagnostics, information technologies and digitization, are enabling more disaggregated value network models that now have the potential to be served economically.

Table 1: Pre-screening of candidates A-F with opportunities identified in terms of SN implications and process/technical feasibility – informing business context

<table>
<thead>
<tr>
<th>Candidate</th>
<th>‘Business’ Context</th>
<th>Clinical Trials</th>
<th>Process &amp; Technology Feasibility</th>
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<tbody>
<tr>
<td>A</td>
<td>Therapy/disease Area: Diabetes. Patient Population: Global estimate in 2010: 385MM people affected, of which 90% is Type 2 i.e. 345MM. Growing in many countries, major healthcare cost e.g. UK-17% of NHS budget; US- circa 20% of overall SS affected with estimated cost burden of $332B; China circa 100MM, growth at ca 30% every 7 years; India, circa 50MM affected and growing rapidly. Treatment: High dose (1000-2000mg/day). Chronic (i.e. lifetime) Stable, growing demand. Cost: Price of a generic pack in US - 120x100mg tablets is ca $150 ($100). In UK 160x50mg tablets cost £27, considerably cheaper (Source: LloydsPharmacy). 150mg tablets being offered for £0.15 each. Estimated API costs circa £10-20/kg Volumes: circa 1000 tonnes/a</td>
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<td>B</td>
<td>Therapy/disease Area: Malaria. Patient Population: circa 160MM, estimated number of courses in 2011 is 278MM (Source: WHO 2012). High volume, stable demand profile. First-line treatment in 76/88 countries where P.falciparum is endemic. Treatment: typically 7-14 days. Cost: Plant-derived ‘B’ costs around $500-600/kg. Still patent protected in US (Novartis). Novartis and SanofiAvantis offer ‘B’ on non-HIV market. Sanofi have a new biosynthesis process and plant (in Italy) eventually capable of producing ca 50 tonnes/year, at a cost of $350-400/kg. Intent is to reduce treatment cost to ca $0.50 per dose Volumes: 300 tonne/a</td>
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<td>C</td>
<td>Therapy/disease Area: HIV. Patient Population: Estimated 15MM need antiretroviral (ART) treatment. Treatment: Number of drugs used is large and segments are complex. Cost: Indian generics and compulsory licensing has driven typical ARV treatment to &lt;$1 per day. Drug costs for older ARVs are $400-1000/kg, whereas newer, and lower volume drugs are &gt;$2000/kg. Volumes: generally 100-1000 tonne/a (estimated) Several ARVs - typical volume demands for API range from 5-10 tonnes/a to 50-100+ tonnes/a</td>
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<td>D</td>
<td>Therapy/disease Area: Inhaled steroid used in respiratory. Patient Population: Stable population (TBC) Treatment: n.x low dose (micro-g) Cost: TBC Volumes: low 50-100 tonne/a</td>
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<td>E</td>
<td>Therapy/disease Area: Veterinary Patient Population: High ‘patient’ population, limited variety Treatment: multiple Cost: TBC Volumes: High circa 100-500 tonne/a</td>
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<td>F</td>
<td>Therapy/disease Area: AgriChem Population n/a Treatment: multiple Cost: TBC Volumes: High, low variety, 10,000 tonne/a (estimate)</td>
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Step B: An Industrial landscape mapping methodology was first developed (integrating value chain analysis with supply network configuration mapping) that is applicable to a broader industrial systems context (Srai and Gregory, 2008; Srai, 2010; Srai et al, 2014). Cross-sector case data suggests that these networks often are comprised of semi-independent sub-systems
that have evolved over extended time periods but have then become part-disconnected, operating as silos of activity with independent governance and coordination mechanisms. Hence, the methodology has been extended to enable exploration of the drivers of, and interactions between, adjacent and dis-connected sub-systems in complex, multi-tier value networks.

The next step of the systems integration approach involves sub-system identification, and definition in terms of the critical metrics used to optimise these semi-independent sub-systems (see figure 2).

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**Figure 2. Potential benefits of CM in the Pharmaceutical industry**

**Table: Conti Impact Variables**

<table>
<thead>
<tr>
<th>Conti Impact Variables</th>
<th>Clinical Trials</th>
<th>Primary</th>
<th>Secondary</th>
<th>Packaging</th>
<th>E2E</th>
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<tr>
<td>Inventory</td>
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<td>Lead time supply</td>
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<td>Lead time to market</td>
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<td>Scale-up (going into)</td>
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<td>Volume flexibility (mix &amp; volume)</td>
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<td>Process control; reliability; safety</td>
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<td>Quality; purity; counterfeiti</td>
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<td>Yield</td>
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<td>IP protection / ext'n/ counterfeiti</td>
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<tr>
<td>Cost (Proc / Pkg / Transport)</td>
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<td>Investment cost</td>
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<td>Fiscal / Tax</td>
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<td>Environmental impact / solvent</td>
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<td>Viability / adoptability</td>
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<td>Asset Utilisation</td>
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**Comment**

- Likely to be benefits from better E2E management given scale, variety and complexity.
- A content high, having a stable API stable API is of core importance to downstream processing – this may offer an advantage for continuous.
- Include generic API to letters of tactical task, not relevant unless part of new combination.
- Current step in emerging strategy not growing, nice experience. No more volume flex.
- Several formulations are available in combination.
- Currently a very simple process, what can CM technology breakthrough bring (e.g. PAT)?
- Further analysis required based on specific chemistry and supporting CM technology to quantify benefits.
- Yield currently circa 96%.

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**Figure 3. Potential benefits – Candidate A**

- Off-patent: Multiple suppliers - counterfeit prevention opportunity - quantify (2)
- Cost (Proc/Pkg/Transport) - Likely already low further analysis required: Some opportunity to improve performance in conti pack around flexibility and service?
- Investment Cost - Growing markets, however currently multiple suppliers. Further analysis required on economic advantages with shift to CM
- Environmental impact/solvent - Further analysis required based on specific CM technology requirements & chemistry routes to manufacture
- Mobility/adaptability - Ease of manufacture (1 step chemistry) - amenable to smaller CM plants? Strength, pack size, country considerations
- Asset Utilisation - Demand likely to be fairly steady but growing. Not seasonal; high volume flex. Several formulations are available in combination
Sub-systems themselves can be identified by current-state supply and value network mapping approaches. This approach identifies the drivers and design factors that predominate in each sub-system. An end-to-end value network performance metric analysis then identified the current state configuration design parameters and trade-offs.

**Step C:** The third stage in the analysis process involves exploring alternative value network scenarios that could emerge by adopting alternative product-process-business model innovation. These alternatives may be based on emerging process and production technologies or even technologies that are still yet to be fully developed (such as continuous processing and crystallization in Pharma). These scenarios may require alternative scale production footprints (dispersed, close-to-market, low-scale integrated plants, for example), or alternative supply models that might now be possible due to advances in ordering or replenishment (such as e-commerce-based last-mile supply chains). In practice, scenarios depend on various disruptive influences that challenge the current value network model and introduce possible product or product-service models.

**Step D:** The final stage is an integrated value network systems analysis that integrates the analysis of the alternative scenarios under consideration, and how they might redefine the sub-systems of the current state configuration (figure 4). The assessment approach, incorporates the potential benefits of given scenarios as a ‘delta’ analysis (%) on the current state for key system metrics, the value proposition in making the transformation from a business context for key value network players (for example, in absolute terms, the potential impact on revenue, margin, inventory reduction etc.) against the investments required, and the technological feasibility of the identified disruption. These three elements of the evaluation are incorporated into a total value network analytical framework (figure 5).

![Figures 4. Sub-system analysis](image-url)
The analytical framework described was deployed to examine the interactions between the value network sub-systems in Pharma (for example, Clinical, Primary/Secondary Manufacturing, Packaging and Distribution, E2E Supply) in order to inform the selection of continuous manufacturing candidates (therapies, patient populations, product-process models). Initial continuous manufacturing candidate profiles were identified, setting out viable business transformation scenarios informed by the value network analysis, integrating inputs on technology readiness from participating technology experts.

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References

